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Green tea and the risk of prostate cancer

A systematic review and meta-analysis

Yuming Guo, MD[a], Fan Zhi, MD[b], Ping Chen, MD[a], Keke Zhao, MD[a], Han Xiang, MD[a], Qi Mao, MD[a], Xinghuan Wang, MD, PhD[a], Xinhua Zhang, MD, PhD[a,*]

Abstract

Prostate cancer (PCa) now remains the 2nd most frequently diagnosed cancer. In recent years, chemoprevention for PCa becomes a possible concept. Especially, many phytochemicals rich foods are suggested to lower the risk of cancer. Among these foods, green tea is considered as effective prevention for various cancers. However, clinical trials and previous meta-analyses on the relationship between green tea consumption and the risk of PCa have produced inconsistent outcomes. This study aims to determine the dose–response association of green tea intake with PCa risk and the preventive effect of green tea catechins on PCa risk. Seven observational studies and 3 randomized controlled trials were retrieved from Cochrane Library, PubMed, Sciencedirect Online, and hand searching. The STATA (version 12.0) was applied to analyze the data. The relative risks (RRs) and 95% confidence intervals were pooled by fixed or random effect modeling. Dose–response relations were evaluated with categories of green tea intake. Although there was no statistical significance in the comparison of the highest versus lowest category, there was a trend of reduced incidence of PCa with each 1 cup/day increase of green tea ($P = 0.08$). Our dose–response meta-analysis further demonstrated that higher green tea consumption was linearly associated with a reduced risk of PCa with more than 7 cups/day. In addition, green tea catechins were effective for preventing PCa with an RR of 0.38 ($P = 0.02$). In conclusion, our dose–response meta-analysis evaluated the association of green tea intake with PCa risk systematically and quantitatively. And this is the first meta-analysis of green tea catechins consumption and PCa incidence. Our novel data demonstrated that higher green tea consumption was linearly reduced PCa risk with more than 7 cups/day and green tea catechins were effective for preventing PCa. However, further studies are required to substantiate these conclusions.

Abbreviations: CI = confidence interval, EGCG = (−)-epigallocatechin-3-gallate, HGPIN = high-grade prostatic intraepithelial neoplasia, HR = hazard ratio, IGF = insulin-like growth factor, OR = odds risk, PCa = prostate cancer, RCT = randomized controlled trial, RR = relative risk.

Keywords: dose–response, green tea, green tea catechins, meta-analysis, prostate cancer

1. Introduction

Prostate cancer (PCa) now remains the 2nd most frequently diagnosed cancer and 5th leading cause of death in men worldwide, with 1.1 million new cases accounting for 15% of new cancer cases overall and 307,500 deaths accounting for 6.6% of total male cancer mortality in 2012.[1] Although the specific cause of PCa remains unclear, genetics is regarded as a specific risk factor for PCa. In addition, environment factors, especially dietary, play significant roles in the initiation and progression of PCa. In recent years, chemoprevention for PCa becomes a possible concept.[2] Especially, many phytochemical-rich foods are suggested to lower the risk of cancer, such as tea, garlic, ginger, berries, and lycopene.[3,4] Among these foods, green tea has been widely used as a PCa preventative.

Green tea is produced from fresh leaves of *Camellia sinensis* by steaming or drying without fermenting. Polyphenols mainly composed of catechins are the main functional extracts from green tea,[5] and the major green tea polyphenol is (−)-epigallocatechin-3-gallate (EGCG) accounting for more than 50% of total polyphenols.[6] Many in vivo and in vitro studies revealed that green tea and its components, especially EGCG, could affect the incidence and the progression of PCa by suppressing proliferation, encouraging apoptosis, preventing invasion and metastasis, and others.[7–10] However, controversy exists among clinical trials. Some epidemiological evidences[11,12] showed protective effect of green tea intake on PCa, while others[13,14] presented null findings with 1 study[15] even showing a tendency of increased PCa risk. Also, previous meta-analyses presented inconsistent findings. A systematic review and meta-analysis by Zheng et al[16] published in 2011 suggested that green tea consumption had a borderline significant decrease of PCa risk for Asian populations. In contrast, another 2 meta-analyses by Lin

Editor: Sumit Arora.

YMG and FZ contributed equally to this work.

Authorship: YMG and FZ contributed equally to this work. YMG, FZ, XHW, and XHZ conceived and designed the study. HX, QM, KKZ, YMG, and PC performed the electronic search, selected studies, extracted data, and performed quality assessment. YMG, FZ, and XHZ analyzed data and conducted meta-analysis. YMG, PC, and XHZ supervised the research, edited and drafted revisions to the article.

The authors have no funding and conflicts of interest to disclose.

[a] Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan, [b] Department of Urology, People's Hospital of New District Longhua, Shenzhen, P.R. China.

[*] Correspondence: Xinhua Zhang, Department of Urology, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan 430071, P.R. China (e-mail: zhangxinhuad@163.com).

Medicine (2017) 96:13(e6426)

Received: 15 August 2016 / Received in final form: 24 February 2017 / Accepted: 27 February 2017

http://dx.doi.org/10.1097/MD.0000000000006426

et al[17] and Fei et al[18] published in 2014 showed no association of green tea intake with PCa. However, these meta-analyses mainly focused on the comparison of highest green tea intake with the lowest or nondrinkers. In fact, the range of green tea intake differed among these studies and the inconsistency might result from different exposure levels and variable content of major functional component EGCG in different green tea.[3] In addition, black tea contains much lower EGCG relative to green tea but most of the previous studies especially some dose–response meta-analyses[19] did not take this into account and focused on the relationship between total tea consumption and PCa risk without further analysis on tea type. Moreover, no systematic review and meta-analysis on the association between EGCG and PCa risk was performed previously. Therefore, we conducted this systematic review to determine the association of green tea intake and PCa risk, with emphasis on the shape of the dose–response curve and relationship between EGCG and PCa risk.

2. Method

2.1. Data sources and searches

We conducted this study based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE). We performed database searches of Cochrane Library, PubMed, and Sciencedirect Online from the date of database inception to February 2016 for all relevant papers published with the following keywords in combination with both medical subject headings terms and text words: green tea or polyphenol or catechin or (−)-epigallocatechin-3-gallate plus prostate cancer or prostate neoplasm or prostate tumor or prostate carcinoma. There was no limitation on language. Reference lists of the included studies were manually checked to identify additional articles.

2.2. Inclusion criteria

Studies were included if they met the following criteria: cohort or case–control studies or randomized controlled trials (RCTs) were included and analyzed accordingly; the intake of green tea or extracts were recorded; the outcome of study should be an incidence of PCa diagnosed by histology, pathology, or histopathology; patients in the case group must be diagnosed as PCa and free of PCa in the control group or the noncase group; the relative risk (RR), odds risk (OR) or hazard ratio (HR) with 95% confidence interval (95% CI), and the number of cases and noncases were reported; and there were at least 3 quantitative categories of green tea in observational studies, and there was no limitation of quantity for RCTs about green tea catechins and PCa risk.

2.3. Exclusion criteria

Repeat publications and studies without classification of the type of tea were excluded.

2.4. Selection of studies

Three investigators (HX, QM, and KKZ) independently screened the titles and abstracts of each article retrieved using a standardized approach to remove duplicate references, reviews, comments, experimental studies, and single case reports. Then 2 independent investigators (YMG and PC) screened the full-text papers for further assessment if the study fulfilled the inclusion criteria and did not meet the exclusion criteria. Any disagreement was resolved through open discussion.

2.5. Quality assess

The Newcastle–Ottawa Scale[20] was used to evaluate methodological quality of observational studies, which consisted of 9 items. When met 1 item, the study got 1 score. In addition, the RCTs were assessed with the Cochrane Collaboration bias appraisal tool. The following factors were evaluated particularly: Adequate sequence generation? Allocation concealment? Binding? Incomplete outcome data addressed? Free of selective reporting? Free of other bias? Where disagreement in opinion existed, they were resolved through open discussion.

2.6. Data extraction

Data were extracted independently by 3 reviewers (YMG, FZ, and PC) using a standard data collection guideline to ensure a consistent approach. The following data were extracted for each included study: first author, publication year, study design, study location, age, duration of follow-up, the numbers of cases/noncases, person-years, intervention, dose categories, adjusted or crude RR, OR, or HR with 95% CI, and adjusted variables. If the data were unavailable from the article, we would contact with the author. Discrepancies were resolved by discussion.

2.7. Statistics analysis

STATA version 12.0 (Stata Corp LP, College Station, TX) was applied to analyze the data. RR and 95% CI across categories of green tea intake were measured as effect size for all studies. HR and OR were approximated to RR because of the low absolute incidence of PCa.[21] The adjusted RR and relevant 95% CI for highest versus lowest category of green tea intake or green tea catechins were pooled, and dose–response analysis was conducted with the method described by Greenland and Longnecher[22] to estimate dose–response trend derived for each study. Then, we estimated the overall RR by combining these trends derived from each study. In addition, we also tested linear and nonlinear associations between green tea intake and PCa risk using restricted cubic splines which was estimated with a generalized least squares regression, with 3 knots at fixed centiles (10%, 50%, and 90%) of the distribution.[23] To derive a linear dose–response curve, the distribution of cases and person-years or noncases and exposure levels in each category of green tea intake was required. For studies just reported the total number of cases or person-years without distribution for exposure categories, we estimated the distribution based on definitions of the quantiles. One study reported green tea intake by cups per month or cups per week, and we regarded these exposure categories as 1/30 or 1/7 cups per day, respectively. If the study did not report the median of each category, we used the mean value of the upper and lower boundaries of each category as calculated midpoint to estimate assigned dose. For the lowest category, lower boundary was assumed to be 0 if it was not provided. For the open-ended upper category, the assigned dose was evaluated as the cut point multiplied by 1.5.[24]

Heterogeneity among studies was assessed with the Q test and the I^2 index statistic. If $P < 0.1$ and $I^2 > 50\%$, it was considered that heterogeneity existed among studies and a random-effect models should be applied. If $P > 0.1$ and $I^2 < 50\%$, fixed-effect

models would be applied. Sensitive analysis and subgroup analysis were performed to evaluate the source of heterogeneity and verified the stability of results. In the sensitive analysis, 1 study was omitted at each turn to evaluate the influence of each study on the results. Subgroup analysis was performed by stratifying study type, region, study quality score, and maximum category. Contour-enhanced funnel plots with Egger linear regression test and Begg rank correlation test were used to evaluate the potential publication bias.

Because all the data used for analyses were extracted from the published studies, the ethical approval and informed consent were not necessary.

3. Result

3.1. Characteristics of included studies

Using database search strategy, a total of 1474 records were retrieved from Cochrane Library, PubMed, and Sciencedirect Online. After reviewing the titles and abstracts, 1447 articles were excluded and 27 articles were further assessed by reviewing the full-text. Finally, 10 articles about the relationship between green tea and PCa risk were included, consisting of 4 cohort studies,[11,13–15] 3 case–control studies,[25–27] and 3 RCTs.[6,28,29] Figure 1 shows the search process. The observational studies which investigated the association between green tea intake and PCa risk included 1435 cases among 96,332 individuals and the 3 RCTs studied the relationship between EGCG and PCa incidence included 87 volunteers in EGCG arms of 179 individuals. Most of the included studies were performed in Asia including 1 from Singapore,[13] 4 from Japan,[11,14,15,26] and 1 from China.[27] The rest studies were from other regions including 2 from Europe,[6,29] 1 from North America,[28] and 1 from Africa. [25]Tables 1 and 2 described details of the included studies.

3.2. Quality assess

The quality of observational studies was assessed by the Newcastle-Ottawa Scale, and the quality of RCTs was evaluated by the Cochrane Collaboration bias appraisal tool. As shown in Table 1, all the observational studies are high quality evidences with a score of 7 or 8 except 1 case–control study with a score of 5. All the 3 RCTs did not provide detailed allocation methods, and only 1 study reported the randomization method. Blinding assessment for all the RCTs was judged as positive. For the assessment of incomplete outcome data, only 1 study did not report withdrawal information or reasons. In the assessment of selective reporting and other bias, all 3 RCTs got positive because none risk was detected in both aspects.

3.3. Green tea intake and risk of PCa

A total of 7 observational studies including 4 cohort studies and 3 case–control studies investigated the relevant risk of PCa with green tea intake. As shown in Fig. 2, the overall pooled RR of the highest versus lowest category of green tea intake was 0.75 (95% CI 0.53–1.07) for all studies, 0.977 (95% CI 0.80–1.19) for cohort studies, and 0.453 (95% CI 0.25–0.82) for case–control studies. There was no statistical significance in the comparison of the highest versus lowest category. Because of the high heterogeneity ($I^2=70.3\%$, $P=0.003$), sensitivity analysis was performed. Most studies did not influence the result when excluded sequentially, except 1 case–control study conducted by Jian et al.[27] After this study was excluded, the pooled RR for all studies changed to 0.92 (95% CI 0.77–1.11) with no heterogeneity ($I^2=0\%$, $P=0.46$) and the RR for case–control studies became 0.623 (95% CI 0.368–1.056). However, no statistical significance was found either.

Dose–response meta-analysis was further carried out. As shown in Fig. 3, each 1 cup/day increase of green tea intake

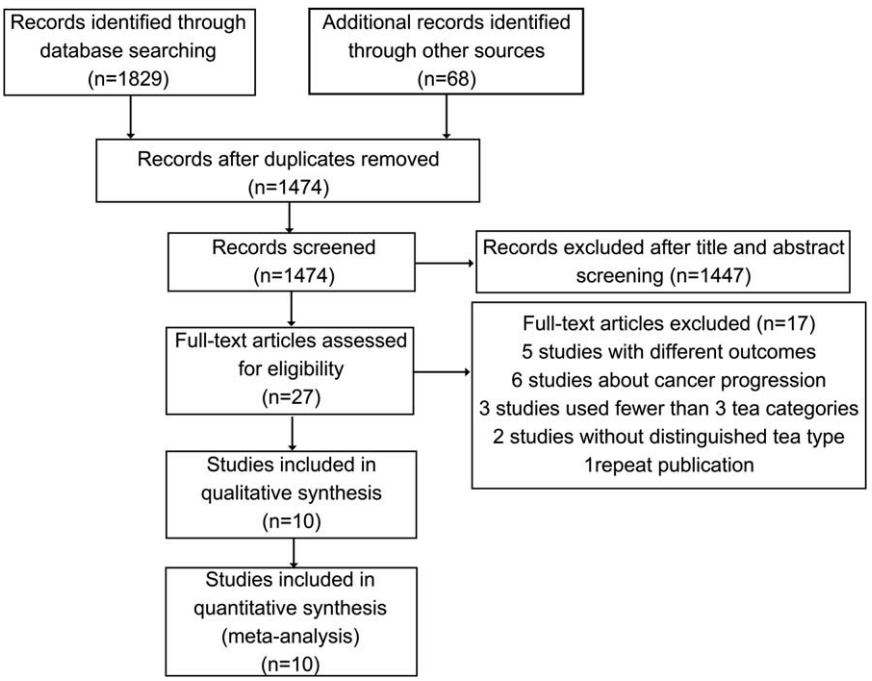

Figure 1. Flowchart of literate searches.

Table 1

Characteristics of studies on tea consumption and prostate cancer risk and quality assessment of eligible studies in meta-analysis.

Author, year	Population, region	Study type	Tea consumption	RR (95%CI)	Adjustments	Quality score
Montague et al, 2012	Chinese, Singapore	Cohort	None	1	Age, dialect group, interview year, education, body mass index, smoking history, and black tea intake	8
			1–3 cups/month	1.07 (0.73, 1.56)		
			1–6 cups/week	1.09 (0.80, 1.48)		
			1 cup/day	1.22 (0.82, 1.82)		
			≥2 cups/day	0.95 (0.62, 1.45)		
Berroukche et al, 2012	Algerian, Algeria	CC	≤1 cup/day	1	Total energy intake, tobacco smoking, and family history of PCa	7
			2–3 cups/day	1.4 (0.8, 2.2)		
			4–6 cups/day	0.9 (0.5, 1.4)		
			>6 cups/day	0.6 (0.3, 1.1)		
Kurahashi et al, 2008	Japanese, Japan	Cohort	<1 cup/day	1	Age, area, smoking status, body mass index, marital status, and alcohol, coffee, black tea, and miso soup consumption	7
			1–2 cups/day	0.98 (0.70, 1.37)		
			3–4 cups/day	0.95 (0.69, 1.30)		
			≥5 cups/day	0.90 (0.66, 1.23)		
Kikuchi et al, 2006	Japanese, Japan	Cohort	<1 cup/day	1	Age, body mass index, smoking status, marital status, daily calorie and calcium intake, alcohol consumption, walking duration, consumption frequencies of black tea, coffee, meat, and fish	8
			1–2 cups/day	0.77 (0.42, 1.40)		
			3–4 cups/day	1.15 (0.69, 1.94)		
			≥5 cups/day	0.85 (0.50, 1.43)		
Sonoda et al, 2004	Japanese, Japan	CC	≤1 cup/day	1	Cigarette smoking and energy intake	5
			2–4 cups/day	0.99 (0.48, 2.03)		
			5–9 cups/day	0.79 (0.38, 1.63)		
			≥10 cups/day	0.67 (0.27, 1.64)		
Jian et al, 2004	Chinese, China	CC	<1 cup/day	1	Age, locality, education, family income, marital status, family history of prostate cancer, physical activities, body mass index, fat intakes, and calories	7
			1–3 cups/day	0.53 (0.30, 0.94)		
			>3 cups/day	0.27 (0.15, 0.48)		
Allen et al, 2004	Japanese, Japan	Cohort	<1 time/day	1	Age, calendar period, city of residence, radiation dose, and education level	7
			2–4 times/day	1.03 (0.69, 1.55)		
			>5 times/day	1.29 (0.84, 1.98)		

CC = case–control study, CI = confidence interval, RR = relative risk.

decreased the risk of PCa with RR 0.954 (95% CI 0.903–1.009) for all studies, 0.989 (95% CI 0.957–1.023) for cohort studies, and 0.893 (95% CI 0.796–1.002) for case–control studies. No statistical significance was found with the dose–response RR estimates. And high heterogeneity ($I^2 = 71.2\%$, $P = 0.002$) was found for all studies. Again, there was no longer any significant heterogeneity ($I^2 = 0\%$, $P = 0.44$) after removing the study by Jian and the pooled RR changed to 0.977 (95% CI 0.951–1.003, $P = 0.080$) with borderline significance for all studies. Moreover, the pooled dose–response estimate (RR 0.956, 95% CI 0.916–0.998) for case–control studies became statistically significant without study of Jian but there was no change for the result of cohort studies.

The linear test indicated there was a linear relationship ($P = 0.01$) between green tea intake and risk of PCa, which demonstrated green tea consumption might reduce the incidence of PCa with a linear dose–response effect. And no evidence of a potential nonlinear relationship ($P = 0.57$) was found. The approximate RRs of each dose of green tea intake were as follows: 0.95 (95% CI 0.81–1.10) for 3 cups, 0.88 (95% CI 0.74–1.04) for 5 cups, 0.81 (95% CI 0.67–0.97) for 7 cups, 0.74 (95% CI 0.59–0.93) for 9 cups, and 0.56 (95% CI 0.35–0.92) for 15 cups. As shown in Fig. 4, the risk of PCa decreased dose dependently with the increase of green tea intake and there was statistically significant decrease of PCa risk with higher green tea consumption (more than 7 cups/day). Subgroup analysis was further performed by study type, region, study quality score, and maximum category. When stratified by study type, the case–control studies indicated a protective effect of green tea intake against PCa for both highest versus lowest category (RR = 0.453, 95% CI 0.249–0.822) and each 1 cup/day increase of green tea (RR = 0.893, 95% CI 0.796–1.002, $P = 0.054$). However, the pooled RR did not differ substantially in other subgroups (Tables 3 and 4).

Table 2

Characteristics of studies on green tea catechins and prostate cancer risk.

Author, year	Region	Sample size	Inclusion criteria	Intervention	Control	Treatment period
Kumar et al, 2015	USA	97	HGPIN or ASAP	EGCG 400 mg	Placebo	12 months
Brausi et al, 2008	Italy	22	HGPIN	Green tea catechins 600 mg/day	Placebo	30 months
Bettuzzi et al, 2006	Italy	60	HGPIN	Green tea catechins 600 mg/day	Placebo	12 months

ASAP = atypical small acinar proliferation, EGCG = (−)-epigallocatechin-3-gallate, HGPIN = high-grade prostatic intraepithelial neoplasia.

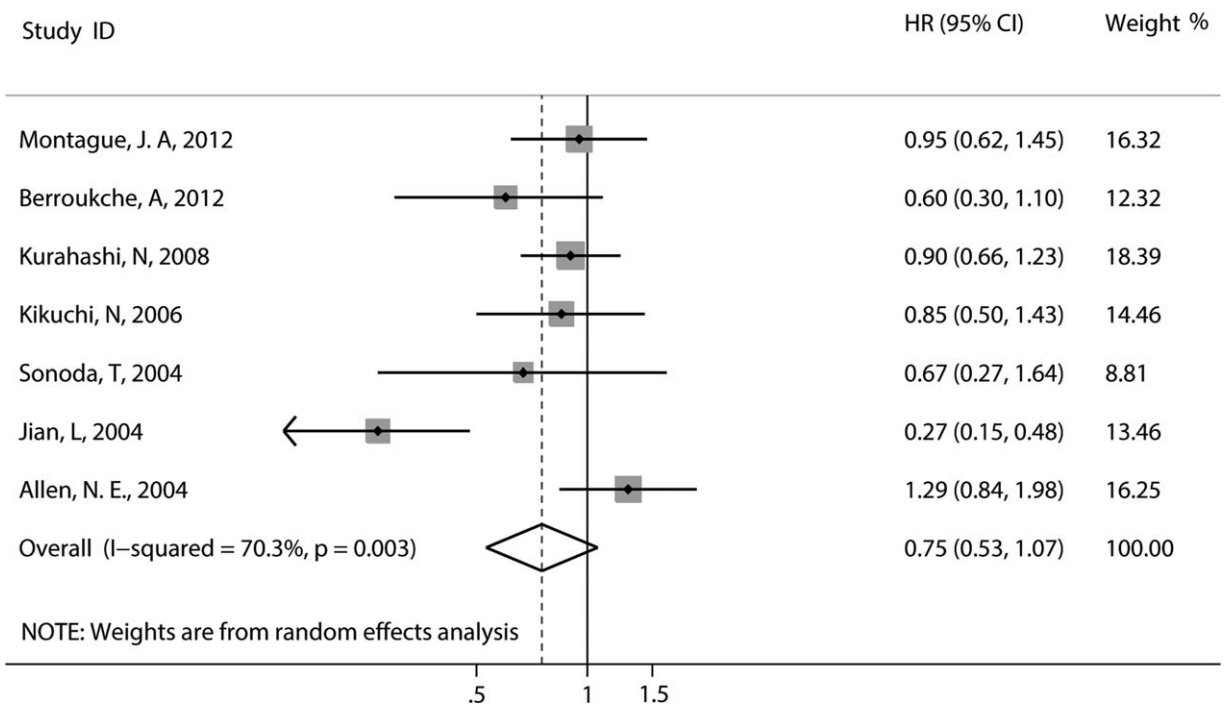

Figure 2. Forest plot for the association of highest versus lowest category of green tea intake and PCa. The association was indicated as RR with the corresponding 95% CI. The RR estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. RR < 1 indicates decreased risk of PCa. CI = confidence interval, PCa = prostate cancer, RR = relative risk.

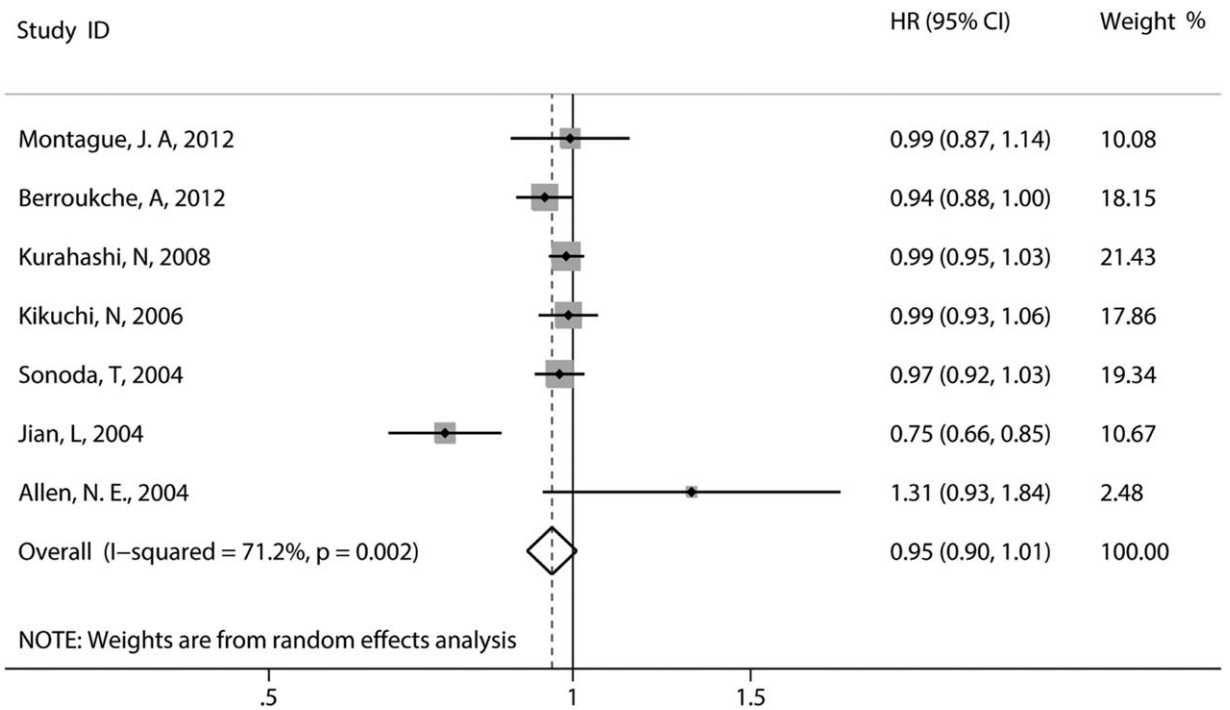

Figure 3. Forest plot for the association of each 1 cup/day increase of green tea intake and PCa. The association was indicated as RR with the corresponding 95% CI. The RR estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. RR < 1 indicates decreased risk of PCa. CI = confidence interval, PCa = prostate cancer, RR = relative risk.

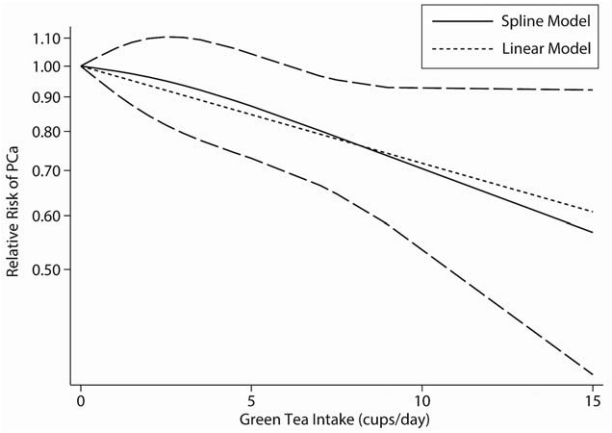

Figure 4. Dose–response analysis of green tea consumption and the risk of PCa. The solid black line and 2 dotted black lines are the restricted cubic spline for the published RRs and 95% CIs; the short dash straight line is the linear fitting curve used for linear and nonlinear analysis. CI = confidence interval, PCa = prostate cancer, RR = relative risk.

3.4. Green tea catechins and risk of PCa

Only 3 RCTs were included to investigate the association of green tea catechins with the risk of PCa. And the study populations were patients with high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP). PCa incidence was the main outcome of these studies. The I^2 standing for heterogeneity was 2.9% which indicated there was no heterogeneity among the included trials, and a fixed-effect model was used. As shown in Fig. 5, green tea catechins had a significant effect on the reduction of PCa risk compared to placebo with an RR of 0.38 (95% CI 0.16–0.86, $P = 0.02$), indicating green tea catechins could reduce the PCa risk in patients with HGPIN or ASAP significantly. Because of the insufficient quantity of the studies, neither subgroup analysis nor dose–response analysis was conducted in these RCTs of green tea catechins and PCa risk.

3.5. Publication bias

No obvious publication bias was detected in our studies by Begg rank correlation test and Egger linear regression test in the meta-analysis of highest versus lowest category green tea intake (P for Begg test = 0.23, P for Egger test = 0.26), dose–response meta-analysis of each 1 cup/day increase of green tea (P for Begg test = 0.74, P for Egger test = 0.88), and the meta-analysis of green tea catechins and PCa risk (P for Begg test = 0.45, P for Egger test = 0.60).

Table 3

Study subgroup analysis of pooled risk estimates for highest versus lowest green tea intake and PCa.

	Studies (n)	RR (95% CI)	Test for heterogeneity I^2	Test for heterogeneity P
Study type				
Cohort	4	0.977 (0.800, 1.194)	0	0.538
CC	3	0.453 (0.249, 0.822)	54.5%	0.111
Region				
Asian	6	0.774 (0.526, 1.141)	74.0%	0.002
Non-Asian	1	0.600 (0.313, 1.149)	–	–
Study quality score				
≥8	2	0.909 (0.653, 1.265)	0	0.747
<8	5	0.682 (0.406, 1.143)	79.6%	0.001
Maximum category				
≥5 cups/day	4	0.825 (0.531, 1.066)	0	0.696
<5 cups/day	3	0.708 (0.307, 1.633)	89.3%	<0.001

CC = case–control study, CI = confidence interval, PCa = prostate cancer, RR = relative risk.

Table 4

Study subgroup analysis of pooled risk estimates for each 1 cup/day increase of green tea intake and PCa.

	Studies (n)	RR (95% CI)	Test for heterogeneity I^2	Test for heterogeneity P
Study type				
Cohort	4	0.989 (0.957, 1.023)	0	0.441
CC	3	0.893 (0.796, 1.002)	84.9%	0.001
Region				
Asian	6	0.956 (0.893, 1.024)	74.8%	0.001
Non-Asian	1	0.938 (0.879, 1.002)	–	–
Study quality score				
≥8	2	0.991 (0.933, 1.053)	0	0.958
<8	5	0.938 (0.868, 1.014)	80.0%	<0.001

CC = case–control study, CI = confidence interval, PCa = prostate cancer, RR = relative risk.

4. Discussion

To our knowledge, this is the first meta-analysis of green tea catechins consumption and PCa incidence. Also, we conducted a dose–response meta-analysis to systematically and quantitatively evaluate the association of green tea intake with PCa risk. Our novel data demonstrated green tea consumption might reduce the incidence of PCa with a linear dose–response effect and more than 7 cups/day intake significantly decreased the PCa risk and green tea catechins might be effective for preventing PCa.

Although previous meta-analyses found no association between PCa risk and green tea intake, limitations in these studies might affect the conclusion. First, among the included studies in these meta-analyses, the highest green tea consumption level varied from "ever drunk" to "more than 10 cups/day." The inconsistent exposure levels probably would bias the results. In addition, catechins content in black tea is approximately a 3rd of that in green tea due to the process of fermentation, which might lead to different effect on PCa. However, the dose–response meta-analysis conducted by Fei et al[18] did not take this into account. Finally, our study has appended 2 additional articles compared with previous meta-analysis by Zheng et al,[16] which would strengthen the current conclusion.

Consistent with pervious meta-analyses by Lin et al[17] (RR = 0.79, 95% CI 0.43–1.14) and Fei et al[18] (RR = 0.73, 95% CI 0.52–1.02), no significant inverse association was found between green tea intake and PCa risk when comparing the highest with the lowest dose. Moreover, no statistical significance was found for the dose–response meta-analysis of each 1 cup/day increase of green tea intake on PCa risk of the 7 included observational studies. However, significant heterogeneity existed and sensitivity analysis showed the heterogeneity mainly caused by the study of Jian et al,[27] which was carried out in China in the population drinking green tea longer than 40 years and indicated a significant decrease of PCa risk with green tea intake. But most studies did not provide the duration of tea consumption. After removing the study of Jian, there was no longer any significant heterogeneity and dose–response analysis demonstrated a trend that each 1 cup/day increase of green tea intake decreased PCa

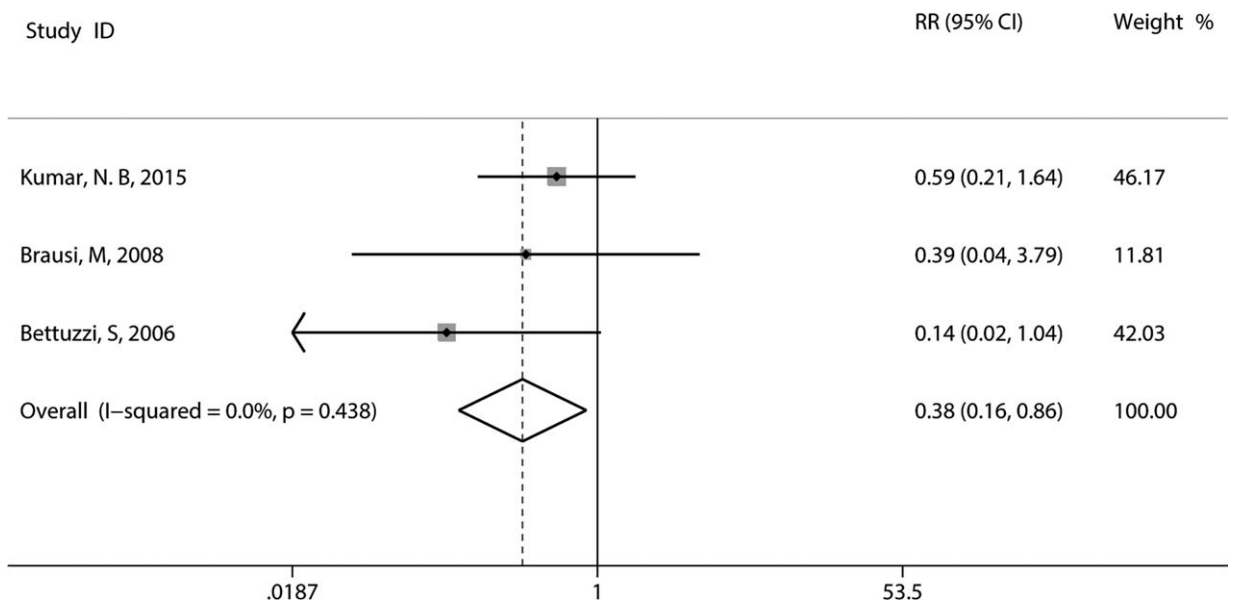

Figure 5. Forest plot for the association of green tea catechins and PCa. The association was indicated as RR with the corresponding 95% CI. The RR estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. RR < 1 indicates decreased risk of PCa. CI = confidence interval, PCa = prostate cancer, RR = relative risk.

risk by 4.5% ($P = 0.08$). In addition, our dose–response meta-analysis indicated more than 7 cups/day green tea consumption could significantly reduce the risk of PCa in a linear style, which was in contrast with previous dose–response meta-analyses[18,19] on the association of PCa risk and total tea consumption without distinguished tea type. Although more green tea intake accounted for lower PCa risk, increased hepatotoxicity was reported with increased green tea intake in a fasting state animal model.[30] Therefore, the Food and Drug Administration restricted EGCG (the major functional extracts of green tea) to 400 mg per day.[28] The ideal daily intake of green tea is unknown, although pharmacokinetic studies suggested 9 to 16 cups per day to be safe and well tolerated.[31] Additionally, in the subgroup analysis stratified by the study type, the 3 case–control studies presented statistically significant inverse association between PCa risk with green tea intake, while the 4 cohort studies showed null effect. But the association did not differ substantially between subgroups stratified by region, study quality, and the maximum category.

As the size of cup and the quantity of green tea leaves used per batch differed, long-term green tea intake cannot be accurately estimated. Green tea catechins, the main bioactive constituent of green tea,[5] significantly affected the ability of green tea on cancer prevention and their content varied considerably among different kinds of green tea. Different studies[32,33] reported the content of catechins varied from 14 to 31 g in 100 g green tea. Therefore, catechins might provide a more accurate estimation of green tea intake. Indeed, EGCG (the major functional extracts of green tea) could reduce near 60% risk of PCa in men with ASAP or HGPIN which is a premalignant lesion of PCa. As there were only 3 green tea catechins RCT included in current review and only 1 quantitative category was used in each RCT, subgroup and dose–response analysis were not performed.

The mechanisms of EGCG anticancer activity have been investigated widely. Many studies[34,35] indicated EGCG treatment reduced PCa cell proliferation in vivo and in vitro through androgen and insulin-like growth factor (IGF) pathway. Ren et al[34] found EGCG acted on androgen receptor promoter, decreasing androgen receptor expression and inhibiting cell growth in LNCaP cell. Similar results were observed in the transgenic adenocarcinoma of mouse prostate mice prostate.[35] EGCG also inhibited the critical enzyme 5α-reductase, leading to growth inhibition of prostate tumor.[36] In addition, IGF-1 and IGF-1 receptor expression reduced in EGCG treated animals[35,37] and IGF-induced growth of PCa cells was inhibited by EGCG treatment.[38] Apoptosis in PCa cells is also regulated by EGCG. Kazi et al[39] found EGCG phosphorylated B-cell lymphoma-extra large, leading to cytochrome C release and caspase activation in PCa cells. EGCG reduced nuclear factor kappa-light-chain-enhancer of activated B cells p65 expression and negative regulation of nuclear factor kappa-light-chain-enhancer of activated B cells activity triggered a change in Bax-Bcl-2 ratios and resulted in PCa cell apoptosis.[40,41] EGCG also reduced matrix metalloproteinases which contribute to PCa metastasis.[42] Additionally, vascular epidermal growth factor expression was observed decreased by EGCG treatment in PCa cells,[43] transgenic adenocarcinoma of mouse prostate mice,[44] and PCa cell xenografts in nude mice,[45] indicating angiogenesis required for tumor growth, survival, and metastasis is regulated by EGCG. Moreover, cell-cycle arrest and proteasome inhibition are involved in anticancer perspective of EGCG. The included studies consist of 4 cohort studies, 3 case–control studies, and 3 RCTs. The overall quality is acceptable. The studies of Berroukche et al and Sonoda et al[25,26] did not adjust the RR with age which was considered as a relevant risk factor of PCa. This might lead to bias. Although the protective effect of green tea on PCa risk might be related to the stages of PCa, the further analysis was limited because only 1 cohort study in Japan reported the RR of PCa based on different stages. In addition, the duration of tea consumption might also affect the risk of PCa. But most studies did not provide the duration of tea consumption and more evidences would be needed to further analyze and draw a conclusion.

Heterogeneity was observed in the meta-analysis of observational studies, and sensitivity analysis showed the heterogeneity was mainly caused by the study of Jian et al.[27] This study was performed in China where green tea consumption is higher and more regular among participants. And the cup used in China was generally larger than other countries and the size of cup varied widely. Furthermore, genetic variability in the metabolism of green tea catechins might lead to the difference. A study[46] in Shanghai, China showed men with homozygous for low-activity associated catechol-O-methyltransferase genotype had significant 44% lower urinary level of tea polyphenols than men with homozygous for high-activity catechol-O-methyltransferase genotype. Other possible reasons for the heterogeneity might be different infusion temperature of tea, different drinking behavior (with or without milk and sugar), and varied duration of green tea consumption.

Several limitations in our study should also be concentrated. Detailed information on cup size, quantity of tea leaves used per batch, tea drinking duration, and PCa stages were not provided in most studies, which probably would influence the protective effect of green tea. In addition, potential confounding factors could not be completely avoided in observational studies, especially in retrospective studies.

5. Conclusion

In summary, our meta-analysis indicated green tea intake might reduce the incidence of PCa with a linear dose–response effect and decrease PCa risk significantly with over 7 cups/day. This was further confirmed by the potential protective effect of green tea catechins on PCa. Further prospective study with accurate measurement of green tea intake is required to substantiate these conclusions.

Acknowledgements

The authors thank Yi Guo who is an epidemiologist at school of public health in Wuhan University for his help to guide and ensure all analysis.

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